



(12) **United States Patent**  
**Kilbourn et al.**

(10) **Patent No.: US 6,350,729 B1**  
(45) **Date of Patent: \*Feb. 26, 2002**

(54) **INHIBITION OF NITRIC OXIDE-MEDIATED  
HYPOTENSION AND SEPTIC SHOCK WITH  
IRON-CONTAINING HEMOPROTEIN**

(75) Inventors: **Robert G. Kilbourn**, Houston, TX  
(US); **Joseph De Angelo**, Hamtramck,  
MI (US); **Joseph Bonaventura**,  
Beaufort, NC (US)

(73) Assignees: **Board of Regents, The University of  
Texas System**, Austin, TX (US); **Apex  
Bioscience, Inc.**, Research Triangle  
Park; **Duke University**, Durham, both  
of NC (US)

(\*) Notice: Subject to any disclaimer, the term of this  
patent is extended or adjusted under 35  
U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-  
claimer.

(21) Appl. No.: **09/615,353**

(22) Filed: **Jul. 13, 2000**

#### Related U.S. Application Data

(63) Continuation of application No. 09/204,392, filed on Dec. 2,  
1998, now Pat. No. 6,103,690, which is a continuation of  
application No. 08/942,632, filed on Oct. 2, 1997, now Pat.  
No. 5,900,403, which is a continuation of application No.  
08/184,255, filed on Jan. 18, 1994, now Pat. No. 5,674,836,  
which is a continuation of application No. 07/838,603, filed  
on Feb. 19, 1992, now Pat. No. 5,296,466.

(51) **Int. Cl.<sup>7</sup>** ..... **A61K 38/42**

(52) **U.S. Cl.** ..... **514/6; 514/12; 514/21;**  
424/85.2; 530/385

(58) **Field of Search** ..... 514/6, 12, 21;  
424/85.2; 530/385

#### (56) References Cited

##### U.S. PATENT DOCUMENTS

4,061,736 A	12/1977	Morris et al.	424/177
4,584,130 A	4/1986	Bucci et al.	260/112
4,598,064 A	7/1986	Walder	514/6
4,751,068 A	6/1988	Bickar et al.	423/437
5,028,627 A	7/1991	Kilbourn et al.	514/565
5,082,642 A	1/1992	Bickar et al.	423/402
5,296,466 A	3/1994	Kilbourn et al.	514/6
5,334,706 A	8/1994	Przybelski	530/385
5,480,866 A	1/1996	Bonaventura et al.	514/6
5,510,464 A	4/1996	Przybelski	530/385
5,674,836 A	10/1997	Kilbourn et al.	514/6
5,900,403 A *	5/1999	Kilbourn et al.	514/6
6,103,690 A *	8/2000	Kilbourn et al.	514/6

##### FOREIGN PATENT DOCUMENTS

WO	91/04024	4/1990
WO	90/02654	7/1990
WO	91/04023	4/1991
WO	91/84023	4/1991
WO	93/00893	1/1993

#### OTHER PUBLICATIONS

Aisaka et al., "N<sup>G</sup>-Methylarginine, an Inhibitor of Endothe-  
lium-Derived Nitric Oxide Synthesis, is a Potent Pressor  
Agent in the Guinea Pig: Does Nitric Oxide Regulate Blood  
Pressure in Vivo?" *Biochemical and Biophysical Research  
Communications*, 160(2):881-886, 1989.

Aranow et al., "Effect of Human Hemoglobin on Systemic  
and Regional Hemodynamics in a Porcine Model of Endot-  
oxemic Shock," *Crit. Care Med.*, 24(9):807-814, 1996.

Baur, "The Evolution of Methaemalbumin," *Comp. Bio-  
chem. Physiol.*, 30:657-664, 1969.

Bickar et al., "Carbon Monoxide-Driven Reduction of Fer-  
ric Heme and Heme Proteins," *Journal of Biological Chem-  
istry*, 259(17):10777-10783, 1984.

Bone, "A Critical Evaluation of New Agents for the Treat-  
ment of Sepsis," *JAMA* 266(12):1686-1691, 1991.

Bone et al., "Comparison of Different Doses of Pyridoxalat-  
ed hemoglobin Polyethylene Conjugate in the Treatment of  
Hyperdynamic Sepsis," *Society of Critical Care Medicine  
Conference*, New Orleans, Feb. 5-9, 1996.

Bone et al., "Effects of Nitric Oxide Scavenging on Sheep  
Pancreas and Liver During Sepsis," *Experimental Biology  
'96, Annual meeting of professional Research Scientists*,  
Washington, D.C., Apr. 14-17, 1996.

Bone et al., "Hemodynamic Effects of Nitric Oxide Synthase  
Inhibition and Nitric Oxide Scavenging in Endotoxemic  
Sheep," *International Anesthesia Research Society, 71st  
Clinical and Scientific Congress*, San Francisco, California,  
Mar. 14-18, 1997.

Bone et al., "Hemodynamic Effects of Pyridoxalated Hemo-  
globin Polyoxyethylene Conjugate (PHP) in Conscious  
Sheep During Septic Shock," *American Society of Anesthe-  
siologist*, Atlanta, 1995.

Bone et al., "Nitric Oxide Synthase Inhibition Versus Nitric  
Oxide Scavenging in Sepsis," *68th Scientific Sessions of the  
American Heart Association*, Anaheim, California, Nov.  
13-16, 1995.

Bone, "The Pathogenesis of Sepsis," *Ann. Int. Med.*  
115:457-469, 1991.

Bonkovsky et al., "Intravenous Heme-Albumin in Acute  
Intermittent Porphyria: Evidence for Repletion of Hepatic  
Hemoproteins and Regulatory Heme Pools," *The American  
Journal of Gastroenterology*, 86(8):1050-1056, 1991.

(List continued on next page.)

Primary Examiner—Chhaya D. Sayala

(74) Attorney, Agent, or Firm—Fulbright & Jaworski LLP

#### (57) ABSTRACT

The invention is directed to a method for the prophylaxis or  
treatment of an animal for deleterious physiological effects  
such as systemic hypotension caused by nitric oxide pro-  
duction induced by a biological response modifier.  
Examples of such biological response modifiers include but  
are not limited to a cytokine and an endotoxin. The invention  
is also directed to a method for the treatment of septic shock.

**16 Claims, 1 Drawing Sheet**